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(54) Title: EPROSARTAN MONOHYDRATE

(57) Abstract

This invention relates to (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate, compositions containing the compound and methods of using the compound to block angiotensin II receptors and to treat hypertension, congestive heart failure and renal failure.

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Eprosartan Monohydate

Field of the Invention

This invention relates to a pharmaceutically active compound, compositions containing the compound and methods of using the compound in the treatment of certain disease states in mammals, in particular man. More specifically, the present invention relates to (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate, compositions containing this compound, and methods of using (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate to block angiotensin II (AII) receptors and to treat hypertension, congestive heart failure and renal failure.

Background of the Invention

The compound (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate is known by the name "eprosartan" and is the subject of U.S. Patent No. 5,185,351 (the '351 patent), issued February 9, 1993. This patent discloses in Example 41 a process for making the anhydrous form of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate. Additionally, the '351 patent discloses conventional techniques for formulating (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate and Examples 108-111 specifically detail the preparation of certain formulations. This compound is claimed to have utility in blocking angiotensin II receptors and to be useful in the treatment of hypertension, congestive heart failure and renal failure.

It has been found that the monohydrate of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate is formed during the vacuum drying of the dihydrated form of this compound or when the anhydrate of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate is granulated with water, stored at 50°C overnight and vacuum dried overnight at ambient temperature.

Summary of the Invention

The present invention provides a novel monohydrate of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid

monomethanesulfonate, in particular, in pharmaceutical compositions for the treatment of diseases in which blockade of angiotensin II receptors is indicated, for example, in the treatment of hypertension, congestive heart failure and renal failure.

Brief Description of the Figures

Figures 1, 4 and 7 show, respectively, the thermogravimetric analysis (TGA), the differential scanning calorimetric (DSC) thermogram and the powder X-ray diffraction (XRD) pattern of the anhydrous form of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate.

The anhydrous form of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate exhibits a single thermal event, a melting endotherm at about 250°C associated with a weight loss, suggesting that melting is followed by decomposition of the drug substance (Figure 4). No significant weight loss prior to melting is observed in its TGA [Figure 1], suggesting that this compound does not contain significant quantities of surface adsorbed water and/or residual solvents. The powder X-ray diffraction pattern [Figure 7] exhibits characteristic diffraction lines corresponding to 2θ values of 7, 14, 18.9, 22.2 and 29 degrees.

Figures 3, 6 and 9 show, respectively, the thermogravimetric analysis, the differential scanning calorimetric thermogram and the powder X-ray diffraction pattern of the dihydrated form of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate.

The DSC of the dihydrate [Figure 6] exhibits 3 characteristic endothermic peaks at about 71°C, 99°C and 250°C. The exotherm in Figure 6 at 124°C corresponds to the recrystallization of eprosartan dihydrate to the anhydrate upon dehydration. A typical TGA for the dihydrate exhibits a two-step moisture loss in the temperature range of 25-125°C [Figure 3]. The loss of water associated with the first-step moisture loss begins at 25°C and is essentially complete by 70°C. This weight loss amounts to about 3%, corresponding stoichiometrically to one mole of water per mole of eprosartan anhydrate. The water associated with the second-step moisture loss is lost in the temperature range of 75°-125°C. The dihydrate also exhibits a characteristic powder X-ray diffraction. The XRD [Figure 9] exhibits characteristic diffraction lines corresponding to 2θ values of 8, 10.8, 16.8, 21.9, 26.6 and 30.4 degrees.

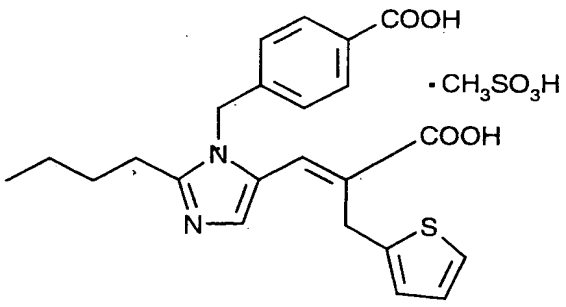
Figures 2, 5 and 8 show, respectively, the thermogravimetric analysis, the differential scanning calorimetric thermogram and the powder X-ray diffraction

pattern of the monohydrate of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate.

The DSC of the monohydrate [Figure 5] exhibits an endothermic peak at about 98°C and an exothermic peak at about 128°C. A typical TGA for the monohydrate exhibits a one-step moisture loss in the temperature range of 25-120°C [Figure 2]. The monohydrate also exhibits a characteristic powder X-ray diffraction [Figure 8].

Detailed Description of the Invention

(E)-α-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate is known to exist in an anhydrous form and is characterized by the data shown in Figures 1, 4 and 7. This compound has the following structure:



(E)-α-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate, eprosartan, is claimed in U.S. Patent No. 5,185,351. Reference should be made to said patent for its full disclosure, including the methods of preparing and using this compound. The entire disclosure of the '351 patent is incorporated herein by reference.

Eprosartan is anhydrous, and, by itself, is stable at ambient temperature and humidity, as well as at accelerated conditions (30°C/79%RH or 40°C/75%RH for up to 6 months). This drug substance does not pick up moisture at higher humidities (typically up to 95%RH). However, the anhydrous form of the compound converts to the hydrated form, if it is moistened prior to storage in a closed container at ambient or higher temperatures, or if the dry powder is stored at a relative humidity of 98% or higher at ambient or higher temperatures for 8 days or longer. In the former case where the hydrate is obtained by moistening the drug substance, the hydrated form is not stable, and is generally converted back into the anhydrous form during drying.

In accordance with the present invention, it has been found that a monohydrated form of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate is produced during the vacuum drying of the dihydrated form of this compound or when the anhydrate of (E)-α-[2-n-butyl-1-[(4-carboxy-phenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate is granulated with water, stored at 50°C overnight and vacuum dried overnight at ambient temperature.

According to the instant invention, the dihydrate prepared using different excipients behave differently in terms of ease of conversion of the dihydrate to the monohydrate during vacuum drying. Continued vacuum drying of moist granulations results in partial to complete conversion of the dihydrate initially formed to the monohydrate. For example, the dihydrate formed in granulations containing excipients, such as soluble starch, xanthan gum and gelatin, stored for for up to 24 hrs, was found to convert to the monohydrate form upon vacuum drying. Eprosartan granulated with water, stored at 50°C overnight and vacuum dried overnight at ambient temperature was also found to be a monohydrate. However, there is always a possibility of getting a mixture of a monohydrate, a dihydrate and an anhydrate depending on the length or severity of vacuum drying.

The two tables, below, summarize the powder X-ray diffraction (XRD) pattern and the FTIR [Fourier transform infrared] spectroscopic data of the anhydrate, the monohydrate and the dihydrate of (E)-α-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate.

Table 1 : Powder X-Ray Data

X-Ray Peak Position, 2θ (Relative Intensity)		
Anhydrate	**Monohydrate**	**Dihydrate**
7.15 (82)	**8.55** (37)	**8.45** (36)
	9.40 (20)	9.95 (20)
		10.80 (22)
13.90 (22)	12.60 (13)	12.35 (14)
14.35 (24)	14.35 (16)	14.00 (15)
	15.80 (35)	15.90 (27)
	17.25 (100)	**16.80** (93)
18.30 (50)	18.25 (58)	18.10 (27)
18.9 (100)	19.25 (43)	18.45 (36)
20.10 (58)	**19.70** (92)	18.70 (40)
20.45 (41)	20.90 (34)	**20.05** (59)
21.00 (44)	21.55 (41)	**20.75** (68)
	21.75 (68)	**21.**45 (81)
22.20 (55)	**22.15** (60)	**21.90 (100)**
	22.60(71)	**22.60 (71)**
	22.90 (79)	
24.35 (43)	**23.45** (84)	**24.**65 (71)
	26.60 (34)	26.60 (35)
	27.25 (38)	27.45 (16)
	28.70 (35)	29.10 (21)
28.95 (21)		
	31.05 (37)	**30.40** (29)
34.20 (8)	35.05 (20)	35.85 (10)

(Note: Characteristic diffraction peaks are highlighted)

Table 2 : FTIR Data

Anhydrate	Monohydrate	Dihydrate
1714	1725	1705
1692	1703	1690
1650	1638	1640
	1613	1614
1539	1534	1538
1505	1504	1511
1429	1419	1438
1384	1379	1384
		1289
1215	1229	1238
1050	1044	1042
851	845	846
712	711	704

(E)-α-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate may be co-administered with other pharmaceutically active compounds, for example, in physical combination or by sequential administration. Conveniently, the compound of this invention and the other active compound are formulated in a pharmaceutical composition. Thus, this invention also relates to pharmaceutical compositions comprising (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate, a pharmaceutically acceptable carrier, and a second pharmaceutically active

compound selected from the group consisting of a diuretic, a calcium channel blocker, a ß-adrenoceptor blocker, a renin inhibitor, and an angiotensin converting enzyme inhibitor. Examples of compounds which may be included in pharmaceutical compositions in combination with (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate are diuretics, particularly a thiazide diuretic, such as hydrochlorothiazide, or a loop diuretic, such as furosemide, calcium channel blockers, particularly dihydropyridine antagonists, such as nifedipine, ß-adrenoceptor blockers, such as propranolol, renin inhibitors, such as enalkinen, and angiotensin converting enzyme inhibitors, such as captopril or enalapril. Preferably, the pharmaceutical composition contains 200-400 mg of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)-methyl]-1H-imidazol-5-yl]methylene-2-thiophene-propionic acid monomethanesulfonate monohydrate in combination with 6.25-25 mg of hydrochlorothiazide.

No unacceptable toxicological effects are expected when (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate is administered in accordance with the present invention.

(E)-α-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate is useful for treating diseases in which blockade of the angiotensin II receptor would be beneficial. Preferably, this compound is used alone or in combination with said second pharmaceutically active compounds in the treatment of hypertension, congestive heart failure and renal failure. Additionally, (E)-α-[2-n-butyl-1-[(4-carboxy-phenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate is of value in the treatment of left ventricular hypertrophy regression, diabetic nephropathy, diabetic retinopathy, mascular degeneration, haemorrhagic stroke, primary and secondary prevention of infarction, prevention of atheroma progression and the regression of atheroma, prevention of restinosis after angioplasty or bypass surgery, improving cognitive function, angina, glaucoma, and CNS disorders, such as anxiety.

The following examples are illustrative of the instant invention. These examples are not intended to limit the scope of this invention as defined hereinabove and as claimed hereinbelow.

In Examples 1-3, below, the term "internals" means the ingredients which are granulated with the anhydrous form of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)-

methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate.

Examples

Examples 1-3

Preparation of (E)-α-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic Acid Monomethanesulfonate Monohydrate

TABLE I

	Example 1 (%)	Example 2 (%)	Example 3 (%)
Internals			
Compound A*	30-50	60-80	50-70
Lactose, hydrous	15-30	7-20	1-5
Cellulose (Avicel)	2-15	7-20	-
Starch 1551	2-7	-	-
Povidone (PVP)	-	2-8	-
Purified water	**	**	**

* (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate, anhydrous form

** Composition does not take into account the formation of the dihydrate during granulation.

Table I, above, summarizes the amounts of Compound A and excipients on a weight for weight basis used in Examples 1-3 below.

Example 1

A fluid bed granulator, UniGlatt, is charged with the anhydrous form of (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate and Impalpable Lactose, homogenized with an aqueous suspension of Starch 1551 and granulated by spraying at a desirable flow rate and dry wet mass to an LOD (loss on drying) of 5.5-6.5% determined using a Sartorius moisture meter tested at 110°C. The monohydrate is formed during the vacuum drying of the dihydrated form of this compound.

Example 2

The internals are premixed in the Collette bowl for 1 min at a low chopper setting and granulated for 4 min by adding water (added in parts) at a high chopper setting. The granulate is then milled through an appropriate screen and dried to an LOD of 5.5-6.5%. The monohydrate is formed during the vacuum drying of the dihydrated form of this compound.

Example 3

The internals are premixed in a high shear granulator and granulated at a high chopper setting with hydrous lactose added in solution. The monohydrate is formed during the vacuum drying of the dihydrated form of this compound.

Example 4

Preparation of (E)-α-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic Acid Monomethanesulfonate Dihydrate

Eprosartan anhydrate was suspended in an aqueous solution of 3.0 M methanesulfonic acid. The suspension was continuously stirred and heated to 65-70°C. The filtrate obtained by suction was maintained at 75°C for several minutes to ensure the absence of the anhydrate in solution. The solution was slowly cooled to ambient temperature and clear colorless crystalline drug substance was harvested by filtration and air dried. The monohydrate is formed during the vacuum drying of the dihydrated form of this compound.

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

What is claimed is:

1. A compound which is (E)-α-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid monomethanesulfonate monohydrate.

2. A pharmaceutical composition comprising the compound according to claim 1, a pharmaceutically acceptable carrier and a second pharmaceutically active compound selected from the group consisting of a diuretic, a calcium channel blocker, a ß-adrenoceptor blocker, a renin inhibitor, and an angiotensin converting enzyme inhibitor.

3.. The pharmaceutical composition according to claim 2 wherein the second pharmaceutically active compound is a diuretic.

4. The pharmaceutical composition according to claim 3 wherein the diuretic is hydrochlorothiazide.

5. The pharmaceutical composition according to claim 2 wherein the second pharmaceutically active compound is a loop diuretic.

6. The pharmaceutical composition according to claim 5 wherein the loop diuretic is furosemide.

7. The pharmaceutical composition according to claim 2 wherein the second pharmaceutically active compound is a calcium channel blocker.

8. The pharmaceutical composition according to claim 7 wherein the calcium channel blocker is nifedipine.

9. The pharmaceutical composition according to claim 2 wherein the second pharmaceutically active compound is a ß-adrenoceptor blocker.

10. The pharmaceutical composition according to claim 9 wherein the ß-adrenoceptor blocker is propranolol.

11. The pharmaceutical composition according to claim 2 wherein the second pharmaceutically active compound is an angiotensin converting enzyme inhibitor.

12. The pharmaceutical composition according to claim 11 wherein the angiotensin converting enzyme inhibitor is captopril or enalapril.

13. The pharmaceutical composition according to claim 2 wherein the second pharmaceutically active compound is a renin inhibitor.

14. The pharmaceutical composition according to claim 13 wherein the renin inhibitor is enalkinen.

15. A method of blocking angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of the compound according to claim 1.

16. A method of treating hypertension which comprises administering to a subject in need thereof an effective amount of the compound according to claim 1.

17. A method of treating hypertension which comprises administering stepwise or in physical combination the compound according to claim 1 and a second pharmaceutically active compound selected from the group consisting of a diuretic, a calcium channel blocker, a ß-adrenoceptor blocker, a renin inhibitor, and an angiotensin converting enzyme inhibitor.

18. The method according to claim 17 wherein the second pharmaceutically active compound is a diuretic.

19. The method according to claim 18 wherein the diuretic is hydrochlorothiazide.

20. The method according to claim 17 wherein the second pharmaceutically active compound is a loop diuretic.

21. The method of claim 20 wherein the loop diuretic is furosemide.

22. The method according to claim 17 wherein the second pharmaceutically active compound is a calcium channel blocker.

23. The method according to claim 22 wherein the calcium channel blocker is nifedipine.

24. The method according to claim 17 wherein the second pharmaceutically active compound is a ß-adrenoceptor blocker.

25. The method according to claim 24 wherein the ß-adrenoceptor blocker is propranolol.

26. The method according to claim 17 wherein the second pharmaceutically active compound is an angiotensin converting enzyme inhibitor.

27. The method according to claim 26 wherein the angiotensin converting enzyme inhibitor is captopril or enalapril.

28. The method according to claim 17 wherein the second pharmaceutically active compound is a renin inhibitor.

29. The method according to claim 28 wherein the renin inhibitor is enalkinen.

30. A method of treating congestive heart failure which comprises administering to a subject in need thereof an effective amount of the compound according to claim 1.

31. A method of treating renal failure which comprises administering to a subject in need thereof an effective amount of the compound according to claim 1.

INTERNATIONAL SEARCH REPORT

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PCT/US98/13459

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 409/06; A61K 31/415
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/315.1; 514/397

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE STRUCTURE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,185,351 A (FINKELSTEIN et al.) 09 February 1993, col. 4, lines 44-46	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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